General

Guideline Title

Lubiprostone for treating chronic idiopathic constipation.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Lubiprostone for treating chronic idiopathic constipation. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 48 p. (Technology appraisal guidance; no. 318).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

- Lubiprostone is recommended as an option for treating chronic idiopathic constipation, that is, for adults in whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and for whom invasive treatment for constipation is being considered.
- If treatment with lubiprostone is not effective after 2 weeks, the person should be re-examined and the benefit of continuing treatment reconsidered.
- Lubiprostone should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, who has carefully reviewed the person's previous courses of laxative treatments specified above.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Chronic idiopathic constipation

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of lubiprostone for treating chronic idiopathic constipation

Target Population

Adult patients with chronic idiopathic constipation in whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and for whom invasive treatment for constipation is being considered

Interventions and Practices Considered

Lubiprostone

Major Outcomes Considered

- Clinical effectiveness
  - Frequency of spontaneous bowel movements
  - Sense of complete evacuation
  - Symptoms of constipation
  - Severity of constipation
  - Use of rescue medication or interventions
  - Adverse effects of treatment
  - Health-related quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this appraisal was prepared by the Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE), Technology Assessment Group, University of York (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches

The manufacturer's submission (MS) described the search strategies used to identify relevant clinical effectiveness studies about the use of lubiprostone (Amitiza®) for the treatment of chronic idiopathic constipation and associated symptoms in adults. Search strategies were only briefly described in the main body of the submission; however, full details were provided in the appendices.

The electronic databases MEDLINE and MEDLINE In-Process (via Ovid), EMBASE (via Ovid), and the Cochrane Library: Cochrane database of systematic reviews (CDSR), register of clinical trials (CENTRAL), National Health Service Health Economic Evaluations Database (NHS HEED), Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effects (DARE), European Network for Health Technology Assessment (EUnetHTA) website, National Institute for Health Research (NIHR) Health Technology Assessment Programme and PROSPERO (International Prospective Register of Systematic Reviews) were searched to identify clinical trials and systematic reviews on the use of lubiprostone and other comparators. To identify on-going or unpublished trials, the following sources were searched and cross-referenced with published articles: National Institutes of Health (NIH) Clinicaltrials.gov, Current Controlled Trials, WHO International Clinical Trials Registry Platform (ICTRP).

Searches were conducted on 16 May 2013 and subsequently updated on 12 December 2013. Search strategies for each database were documented in Section 10.2, Appendix 2 in the MS. In addition, a separate lubiprostone systematic review report provides further details. There were no date limits but they applied language limits, restricting the results to English language. This language limit could be a risk of bias.

Overall the searches were appropriate and well documented, and included the use of both subject indexing terms (MeSH and EMTREE) and free text searching. Field searching, Boolean operators and truncation were used where required. All the databases required by NICE were searched. But not medical society and regulatory body websites were searched.

The search strategies used in the manufacturer's submission were limited to randomised clinical trials (RCTs) applying methodological search filters; however, a search for other study designs such as cohort, case control or single arm studies in general may have provided useful supplementary information about safety. This limitation was recognised in the MS, with the potential that some important single arm studies were missed in the section on safety.

In response to an ERG point for clarification, the manufacturer supplied a list of clinical studies on lubiprostone in idiopathic constipation.

As a point for clarification sent to the manufacturer, the ERG requested a list of all trials (complete or ongoing) of lubiprostone in idiopathic constipation (whatever the formulation or the definition of idiopathic constipation), and all the sponsors own trials and others that were identified by the manufacturer's searches. In response, the manufacturer supplied a list of studies on ClinicalTrials.gov.

The ERG checked the status of these trials on ClinicalTrials.gov. The trials that have already been completed were: NCT01372423, NCT01447849, NCT00934479, NCT01460225.

The ERG searched PubMed, EMBASE and Web of Science (WoS) using these NCT numbers and their authors' names in order to retrieve any publications about these trials. No publications about these trials were retrieved by this search.

Inclusion Criteria

The manufacturer outlined appropriate inclusion criteria for population, interventions and comparators, outcomes and study designs. It is noted that

eligibility criteria for the review did not report that studies that included irritable bowel syndrome (IBS) patients with constipation were excluded. According to the clinical advisor to the ERG, constipation predominant IBS is a similar population to chronic idiopathic constipation (CIC) and it is appropriate to include the constipation predominant IBS population in the trials. The manufacturer included open-label extension studies in addition to RCTs in order to assess long-term safety of lubiprostone. However, the eligibility criteria for the study design only included RCTs.

The search was restricted to English language trials but the ERG does not consider that to be significant.

Study selection was conducted using appropriate methods: study selection was undertaken by two reviewers and discrepancies were resolved by consensus.

Cost-effectiveness

ERG Comment on Manufacturer's Review of Cost-effectiveness Evidence

Searches

The MS described the search strategies used to identify cost-effectiveness studies and utilities relevant to this appraisal of lubiprostone (Amitiza®) for the treatment of CIC and associated symptoms in adults. Search strategies were only briefly described in the main body of the submission, however full details were provided in the Appendices.

The electronic databases MEDLINE and MEDLINE In-Process (via Ovid), EMBASE (via Ovid), the Cochrane Library including CDSR, CENTRAL, HTA, DARE, EUnetHTA website, NIHR Health Technology Assessment Programme, PROSPERO (International Prospective Register of Systematic Reviews) and Econ LIT were searched.

Database searches were performed on 3 December 2013. Search strategies for each database were documented in the Section 10.10, Appendix 10 in the MS. No language or date limits were applied to the search.

No methodological search filters were included to identify economic studies. The manufacturer stated that "To ensure sensitivity, the search strategy was structured to find records which contained only one concept: the intervention, lubiprostone". The manufacturer's search thus excluded cost effectiveness studies related to the comparator technologies unless they were directly compared with lubiprostone. While it could be argued that studies for the comparator technologies may not directly inform the specific question of interest (i.e., the cost-effectiveness of lubiprostone), the ERG considers that this literature may have been helpful in justifying the choice of model structure and in assessments of external validity (i.e., identifying any potential differences in approaches and or assumptions have been employed which may impact on the comparator technologies).

Number of Source Documents

Clinical Effectiveness

Evidence on the clinical effectiveness was taken from 3 phase III randomised controlled trials, 2 phase II dosing studies and 4 open-label studies.

Cost-Effectiveness

The literature review identified 745 records, 573 of which remained after deduplication and were assessed for relevance. From these records, two publications (NIHR HSC 2012 and Canadian Agency for Drugs and Technologies in Health 2007) were reported to have been selected by the manufacturer for review of the full text. Neither reported any evidence relating to the cost-effectiveness of lubiprostone. The manufacturer submitted a *de novo* economic evaluation.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this appraisal was prepared by the Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE), Technology Assessment Group, University of York (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Critique of Data Extraction

The methods used for data extraction were appropriate to reduce reviewer error or bias, with data entered by one reviewer checked by a second and any discrepancies were resolved by consensus. Adequate data from the five Phase III and II randomised clinical trials (RCTs) (SC0131, SC0232, CC0831, SC9921 and CC0721) were presented in the manufacturer's submission (MS). Very little information on the Rao trial was available to present. It is unclear how data from the included non-RCTs were extracted, as no details were provided in the MS for non-RCT evidence.

Quality Assessment

The manufacturer's quality assessment broadly reflects those of the Cochrane risk of bias tool covering randomisation, allocation concealment, similarity of groups at outset, blinding, different dropout, under-reporting of outcomes and use of intention-to-treat (ITT) analysis. This tool was appropriate; however, it was unclear whether the assessment had been conducted in duplicate. The quality of the Rao trial was not assessed as only an abstract was identified in the systematic review of the literature.

A table of the quality assessment results for the five Phase III and II RCTs was presented in the MS (Table 13), which included the quality criteria specified by NICE. In addition, further details were presented in Appendix 3 in the MS. Although there were some minor inconsistencies between the quality assessment results presented in Table 13 and those presented in Appendix 3, relating to intention-to-treat analysis for the CC0721 trials (which was coded as 'Yes' in Table 13, but 'Yes/Not clear' in Appendix 3). The Japanese trials analyse the Full Analysis Set (FAS) (see Section 4.2.1.6 in the ERG report), which differs from the ITT population by a few patients as the FAS population excludes patients without an observation at the final endpoint.

Quality assessment results were checked by the ERG. The ERG was unable to find the details of the methods of randomisation for CC0721 in the study paper.

The ERG has re-assessed the validity of all RCTs and provides a further critique of these trials in Section 4.2 of the ERG report.

Evidence Synthesis

Meta-analyses were conducted for trial outcomes for two populations: (1) the ITT population, (2) the previously treated population (PTP), the patients that had taken a constipation medication within the 90 days prior to trial enrolment. The previously treated population was considered refractory to laxatives.

For the meta-analysis conducted on the ITT trial populations, the three Phase III randomised controlled trials were included (SC0131, SC0232, and CC0831). For the meta-analysis conducted on the previously treated population, only the two Phase III USA trials were included (SC0131 and SC0232). The Japanese Phase III trial was excluded because patients that had taken a medication within the previous 90 days prior to enrolment were difficult to identify as the information had been recorded in Japanese and some information had not been translated. Both fixed and random effect analyses were conducted. No accurate estimates of between-study variance could be obtained due to the small number of trials. The mean effects were similar between the fixed and random effect analyses because of the limited number of trials, but the confidence intervals had the potential to vary.

I-squared was 0 for the meta-analysis for the ITT population and was 59.9% for the PTP population. But the latter meta-analysis only included two trials and nothing about heterogeneity can be concluded from this.

To supplement the direct evidence of lubiprostone compared to placebo, the manufacturer conducted indirect analyses of lubiprostone compared to prucalopride using the studies identified in this systematic review. The details are reported in Sections 4.3 and 4.4 in the ERG report.

Refer to Section 4 of the ERG report for additional critiques of the manufacturer's submitted clinical effectiveness evidence (see the "Availability of Companion Documents" field).

Cost-effectiveness

ERG's Summary and Critique of Manufacturer's Submitted Economic Evaluation

An overall summary of the manufacturer's approach and signposts to the relevant sections in the MS are reported in Table 23 in the ERG report.

Model Structure

The manufacturer undertook a *de novo* economic evaluation based on a decision model. The analysis presented by the manufacturer uses a five state Markov model. These states do not exclusively reflect patients' health but instead comprise a mixture of health states and treatment states.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on the Evidence for Cost-effectiveness

Availability and Nature of Evidence

The Committee heard from clinical specialists that the structure of the economic model was relevant to the typical treatment pathway in clinical practice. The Committee concluded that the model structure was appropriate to capture the main aspects of chronic idiopathic constipation.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee considered assumptions about the proportion of patients who have colonoscopy as an investigation, discontinuation of treatment, utility values used in the model, and the inclusion of a placebo as a comparator.

The Committee concluded that the clinical assumptions made in the economic model were appropriate.

The Committee concluded there was uncertainty as to the number of people who could be maintained on long-term treatment.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee heard from the clinical specialists that people with severe chronic idiopathic constipation would not have the relatively high utility values observed by Huang et al. (2012). However, the Committee was aware that the experiences of people with severe symptoms as described by the clinical specialists may not be representative of the 'average' patient. As a result of the larger population size and the use of the EuroQol 5 dimension (EQ-5D), the Committee concluded that the utility values derived from Huang et al. were an appropriate and reasonable input into the economic model, although it considered the 'true' difference in utility was likely to be somewhere between those from the studies by Huang et al. and Guest et al. (2008).

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

There are no specific groups for whom lubiprostone is particularly cost effective. The Committee concluded that there was very little difference between the previously treated subgroup and the intention-to-treat population.

What Are the Key Drivers of Cost-effectiveness?

The Committee noted the results of the manufacturer's one-way sensitivity analysis, which showed that the incremental cost-effectiveness ratio (ICER) was most sensitive to the relative efficacy of lubiprostone and prucalopride based on the mean change in frequency of spontaneous bowel movement from baseline at weeks 1–4.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

The Committee considered the incremental cost effectiveness of lubiprostone compared with prucalopride, noting the small absolute difference between lubiprostone and prucalopride in terms of the total cost (£22) and quality-adjusted life years (QALYs) (0.0007) in the probabilistic base case. This resulted in pairwise ICERs compared with placebo that were particularly sensitive in many of the scenario analyses.

The Committee considered the impact of exploratory analyses conducted by the Evidence Review Group (ERG) on the continuous dosing of lubiprostone, different source of utility data and the inclusion of a placebo response in the placebo arm on the ICER.

The Committee noted that the inclusion of continuous dosing of lubiprostone increased the ICER of lubiprostone compared with placebo from £64,646 to £75,808 per QALY gained. The Committee noted the ICER was particularly sensitive to assumptions about the long-term maintenance of health-related quality of life benefits attributed to the short-term placebo response rates seen in the phase III trials.

The Committee considered the impact of different sources of utility data on the ICER and considered the true ICER was likely to be somewhere between that from the study by Huang et al. (ICER for lubiprostone compared with placebo of £75,808 per QALY gained) and that from the study by Guest et al. (ICER for lubiprostone compared with placebo of £30,693 per QALY gained).

The Committee considered the impact of the inclusion of laxative costs and different placebo responses in the placebo arm. It noted that in all

scenarios lubiprostone always dominated prucalopride; however, the ICERs of lubiprostone compared with placebo varied depending on the magnitude and duration of placebo response. The ICER for lubiprostone compared with placebo was 16,061 per QALY gained when the placebo benefit was limited to 2 weeks. When the placebo response was combined with increased utility in the unresolved health state ICERs were £20,256 per QALY gained when a full placebo response rate was assumed and £30,953 per QALY gained when a 50% placebo response rate was assumed.

The Committee considered that the additional scenario analyses demonstrated the ICER for lubiprostone compared with placebo was particularly sensitive. In scenarios where these placebo benefits were considered to be transitory, the ICER for lubiprostone compared with placebo was shown to be lower than the range that would normally be considered cost-effective.

The Committee concluded that, in a fully incremental analysis, there was insufficient evidence to demonstrate that lubiprostone was cost-effective compared with placebo. However, it was sufficiently satisfied that the incremental costs and benefits of lubiprostone compared with placebo were comparable to those for prucalopride compared with placebo.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination:

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of lubiprostone and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from randomised controlled trials, phase II dosing studies, and open-label studies. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of lubiprostone for treating chronic idiopathic constipation

Potential Harms

The summary of product characteristics lists the following adverse reactions for lubiprostone: nausea, palpitations, diarrhoea, abdominal distension, flatulence, abdominal discomfort, abdominal pain, indigestion, oedema (including peripheral), chest discomfort, headache, dizziness, dyspnoea,

hyperhidrosis and hot flushes.

For full details of adverse reactions, see the summary of product characteristics.

Contraindications

Contraindications

For full details of contraindications, see the summary of product characteristics for lubiprostone.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic idiopathic constipation and the doctor responsible for their care thinks that lubiprostone is the right treatment, it should be available for use, in line with NICE's recommendations.
- NICE has developed a costing statement (see also the "Availability of Companion Documents" field) explaining the resource impact of this guidance, to help organisations put this guidance into practice.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report

Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Lubiprostone for treating chronic idiopathic constipation. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 48 p. (Technology appraisal guidance; no. 318).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Jul

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Andrew Stevens (*Chair of Appraisal Committee C*), Professor of Public Health, University of Birmingham; Professor Eugene Milne (*Vice Chair*), Director of Public Health, City of Newcastle upon Tyne; Dr David Black, Medical Director, NHS South Yorkshire and Bassetlaw; David Chandler, Lay Member; Gail Coster, Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust; Professor Peter Crome, Honorary Professor, Dept of Primary Care and Population Health, University College London; Professor Rachel A

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Lubiprostone for treating chronic idiopathic constipation. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 6 p. (Technology appraisal guidance; no. 318). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Giannopoulou C, Rice S, Thirimon MB, Rodriguez-Lopez R, Palmer S, Woolacott N, Spackman E: Lubiprostone for treating chronic idiopathic constipation. A single technology appraisal. CRD and CHE Technology Assessment Group; 2014 Mar. 147 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Lubiprostone for treating chronic idiopathic constipation. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. (Technology appraisal guidance; no. 318). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical

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NGC Status

This NGC summary was completed by ECRI Institute on September 10, 2014.

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